

Wernicke's encephalopathy and alcohol-related disease

Datshana P. Naidoo¹, Ashwin Bramdev² and Kumarasen Cooper²

Departments of ¹Medicine and ²Anatomical Pathology, University of Natal, Medical School, Durban, Republic of South Africa

Summary: A pilot study of 31 consecutive alcohol-related deaths over an 8-month period revealed the presence of histologically diagnosed Wernicke's encephalopathy in 17 cases. Analysis of the clinical records revealed that a disturbance of the mental state was the commonest finding and neurological signs were present in only 2 of the 17 cases (ataxia 1, peripheral neuropathy 1). Analysis of 22 ward admissions for Wernicke's encephalopathy during the same 8-month period revealed that the diagnosis is easily made when neurological deficits (ophthalmoplegia, ataxia) accompany mental changes and when Wernicke's encephalopathy is the predominant illness.

In patients with established alcohol-related disease attention is often directed to the presenting illness so that Wernicke's encephalopathy may easily be overlooked as a cause of deterioration in the mental state in these patients. It is recommended that routine management of patients with alcohol-related disease should include thiamine even if neurological signs are absent.

Introduction

Autopsy findings indicate that midbrain lesions typical of Wernicke's encephalopathy (WE) often occur as a complication of other diseases.¹ The illness may also pass unrecognized as it may not always give rise to the classical syndrome, making it impossible to diagnose during life.² The primary illness in such cases is usually a gastrointestinal disorder in which chronic alcoholism is often a major contributory factor. Excessive alcohol intake is a common problem in our patients, yet few cases of WE come to autopsy. We therefore undertook a pilot study to determine the prevalence of WE in patients dying from alcohol-related diseases and define the clinical presentation of these cases in our hospital.

Material and methods

King Edward VIII Hospital is a teaching hospital with 2000 beds and serves the whole of the region of Natal, Republic of South Africa. During an 8-month period (October 88–May 89) post-mortem brains were examined from 31 Black patients who died from alcohol-related diseases. Two samples were excluded from analysis because of other

disease (meningitis; metastatic carcinoma) in the region of interest. The mamillary bodies were sectioned in the remaining 29 brains and examined histologically. Wernicke's encephalopathy was diagnosed in 17 of the 29 cases and was classified as acute (5), chronic (3) and acute on chronic (9) according to accepted histological criteria.³ This paper describes the clinical presentation in these 17 cases.

During the same study period (October 88–May 89) the hospital records of all patients clinically diagnosed as WE were analysed. There were 24 admissions for WE. Two were excluded from analysis because of associated pathology (subdural haematoma and cerebral infarct). The clinical findings in the remaining 22 admissions (21 patients and one readmission) were analysed according to presenting symptoms, physical findings and laboratory investigations. The diagnosis was based on clinical signs of changes in the mental

Table I Clinical diagnosis in autopsy cases (n = 17)

Cirrhosis with portal hypertension	5
Pancreatitis	4
Cardiac failure	2
Pulmonary tuberculosis	3
Alcoholic hepatitis	1
Pellagra	1
Hypoglycaemia	1

Correspondence: D.P. Naidoo, F.C.P.(SA), M.R.C.P. (UK), Department of Medicine, University of Natal, PO Box 17039, Congella 4013, South Africa
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state with/without ocular palsy, ataxia and peripheral neuropathy. Rapid improvement after therapy with thiamine was regarded as essential confirmatory evidence of the diagnosis since biochemical assay of thiamine status was not performed in any patient. The physical findings in these 22 admissions are also discussed.

Results

Autopsy study

WE was diagnosed in 17 patients (14 males, 3 females). The mean age was 47.2 years (range 31–60). By selection, the underlying disease was alcohol-related, so that patients presented with signs referable to the system involved (Table I). Five patients had previous admissions for alcohol-related disease. Overt signs of avitaminosis (pellagra 2, scurvy 1) were present in 3 of the 17 cases.

The commonest presenting symptom (Table II) that could be attributed to WE was a disturbance in the mental state (9/17) ranging from mental obtundation (2) to confusion (5) and coma (2). Recent vomiting with abdominal pain occurred in 5 patients. Two patients had locomotor symptoms and complained of difficulty in walking. None of the patients presented with visual difficulties. Dyspnoea was common (7/17) and in 2 cases were due to concomitant cardiac failure. Three patients were also diabetic (two with chronic pancreatitis were receiving insulin therapy).

Neither cranial nerve palsy nor nystagmus was documented in any patient. Hence, none had the classical triad of mental confusion, ocular palsy and ataxia. Ataxia was elicited in one of 2 patients who had locomotor difficulty. The second patient also complained of hyperaesthesia of the soles of the feet and had signs of peripheral neuropathy.

Autopsy findings revealed that death could reasonably be attributed to the presenting illness (bleeding varices, acute pancreatitis and liver failure) in 12 patients. The remaining 5 patients had

alcoholic hepatitis, chronic pancreatitis and cardiac failure. WE could have contributed to the death of 5 patients as no life-threatening condition, other than the acute changes of WE, was found at autopsy. Although thiamine was administered in two patients and B-complex vitamins in another two, the diagnosis of WE had not been entertained in any of the 17 patients.

Clinical study

There were 13 males and 8 females (mean age 42.9 years). One patient was readmitted 5 months later with a similar presentation. A feeling of generalized weakness together with an inability to walk was the commonest presenting symptom ($n = 12$). It was associated with calf pain in 3 patients. Ten patients had gastrointestinal symptoms which included abdominal discomfort and vomiting. Overt malnutrition was not a feature (mean serum albumin 37.2 ± 8 g/l); two patients had pellagra. The underlying alcoholic aetiology was confirmed by raised mean red cell volumes. In addition the gammaglutamyl transferase level was elevated (> 2 times normal levels) in 12 patients, all of whom had significant hepatomegaly.

A disturbance of the mental state was observed in 14 patients (66%); 12 were confused and 2 were drowsy. Cranial nerve palsy was documented in 21 patients. The remaining case had postural hypotension. Thirteen patients had an isolated sixth nerve palsy (bilateral in 12). A further 5 patients had a combined sixth and third nerve palsy. Bilateral ptosis (1) and gaze paresis (2) constituted the remainder. When present, third nerve palsies were always partial and spared the pupils.

Eighteen patients (82%) had an ataxic gait; in 8 of these, other signs of limb inco-ordination (finger-nose, dysidiadochokinesis and past-pointing) were also present. Nystagmus, present in 16 patients (73%), was an invariable accompaniment to ataxia. In 5 patients, who had total ophthalmoplegia, nystagmus was absent on admission and appeared as the cranial nerve palsy recovered following treatment; 15 patients had signs of peripheral nerve damage. Signs were gross (loss of ankle and knee jerks with stocking anaesthesia) in the 10 patients who presented with inability to walk as a main complaint.

The cranial palsy recovered almost immediately and had resolved by the next day in 14 cases (67%). A further 5 improved by the 2nd day after admission. Nystagmus and ataxia improved more gradually over 4–5 days with mild residual impairment that persisted for a longer period. In most cases there was immediate improvement in cognitive state but long term follow-up to assess memory was not possible because of lack of compliance.

Table II Presenting manifestations in Wernicke's encephalopathy

	Autopsy ($n = 17$)	Clinical ($n = 22$)
Abnormal mental state	9	14
Vomiting	8	5
Abdominal pain	6	2
Dyspnoea	6	7
Loss of appetite	2	3
Inability to walk	2	14
Neurological deficit	2	21

Discussion

Thiamine deficiency in the Western world has been reported in 30–80% of alcoholics.⁴ Although chronic alcoholism is becoming an increasing problem in the Third World⁵ there is little prospective data on WE from these countries.

In the alcoholic patient many factors contribute to a thiamine-deficient state which may predispose to brain damage.⁶ Intake of thiamine is reduced and absorption impaired by alcohol or malnutrition. Liver disease itself leads to reduced body stores and impaired metabolism of thiamine.⁶ This may partly explain the high prevalence of WE in our study in which 11 patients had severe liver disease. In Harper's autopsy series⁷ of 131 cases 60% had concomitant liver disease; cirrhosis was present in 37% of patients. Similarly, Victor⁸ reported cirrhosis of the liver in 36 out of 81 autopsied cases (44%). In a more recent prospective study, Harper⁹ reported a 2.1% prevalence of WE at autopsy. All 6 cases in his study had cirrhosis of the liver. Although liver disease was a predominant finding by case selection in our autopsy study, hepatomegaly was present in 12 of the clinically diagnosed cases; in 9 of these patients other signs of chronic liver disease were present. It appears that hepatic dysfunction augments the deleterious effect of alcohol on the brain, possibly through an imbalance in amino acid metabolism.¹⁰ In a recent prospective clinical study alcoholic hepatitis was present in all 26 of 32 patients who had a liver biopsy.¹¹ This is not surprising since thiamine is phosphorylated in the liver via hepatic pyrophosphokinase, an enzyme that is inhibited by alcohol.¹²

The lack of clinical documentation supporting a diagnosis of WE, is in keeping with previous autopsy reports.^{3–5} Cravioto¹³ found that the classical triad of features is uncommon, occurring in 4 out of 28 cases diagnosed at autopsy. In contrast, in Harper's series, the classical triad was present in the majority of clinically diagnosed cases. Of the 'undiagnosed' cases only 16% had the classical triad and 19% had no clinical signs documented! In Harper's prospective study,⁹ nystagmus was the only other neurological sign in addition to mental change and was found in two patients. Several factors may account for this: So much attention is directed to the overt clinical problem that a deterioration in the mental state is often attributed directly to the presenting illness, to hypoglycaemia, delirium tremens or hepatic encephalopathy rather than to the development of Wernicke's encephalopathy. Furthermore, less detail is paid to neurological assessment in the alcoholic as this demands a more co-operative patient: the symptom of generalized weakness with inability to walk or confinement to bed may conceal a more specific

gait disturbance (peripheral neuropathy/ataxia). For these reasons a high index of suspicion is required in mentally obtunded or unco-operative patients, especially in those with an alcoholic background.

The lack of clinical signs in autopsy-diagnosed cases has also been attributed to several subclinical attacks of Wernicke's encephalopathy in patients who demonstrate no ocular palsy but a global disturbance in the mental state.⁴ Repeated clinical episodes may well have been transient, with recovery occurring as diet improved during periods of abstinence from alcohol. This may explain the chronic histological changes seen in our autopsy cases. The acute changes seen in our study could have been due to a deficiency state developing in the terminal phase of illness. Five patients presented with abdominal pain and vomiting and a further 2 had haematemesis. Loss of appetite was also a common symptom. Abdominal swelling and pain due either to alcoholic hepatitis or pancreatitis also precluded eating in the last few days prior to admission. All these factors probably contributed to poor food intake in the already malnourished alcoholic with organ failure.

Lastly, several of our patients had been well until sudden unexpected deterioration shortly after admission which could have been related to the iatrogenic intervention of administration of dextrose or dextrose-containing fluids in the management of hypoglycaemia or hepatic encephalopathy. The unbalanced administration of dextrose without concomitant therapy with thiamine may precipitate an acute deficiency state in patients with borderline thiamine stores.⁶ A further distressing finding was the lack of thiamine supplementation in alcoholic patients with repeated admissions (5), overt avitaminosis (3) and heart failure (2). Also, 2 of the 3 diabetic patients were receiving insulin. Treatment of the hyperglycaemic state with insulin or oral sulphonylureas can precipitate acute thiamine deficiency since these agents promote the peripheral uptake of glucose with utilization of the available thiamine stores in the marginally depleted patient.¹⁴

In contrast to the autopsy cases neurological deficit was present in all clinically diagnosed cases. The commonest symptom which caused patients to seek attention was inability to walk ($n = 12$). Ten patients had marked peripheral neuropathy with sensory loss and ataxia. These findings are similar to Victor's series in which 75% presented with ataxia and peripheral neuropathy occurred in 58%. A further interesting finding was the absence of nystagmus in 5 patients who had almost total ophthalmoplegia from combined third and sixth nerve palsies. Nystagmus appeared as eye movements returned after therapy was instituted.

In conclusion, it appears that Wernicke's encephalopathy

phalopathy is easily diagnosed when neurological deficits accompany mental changes, and when it is the sole presenting illness. This entity is a common accompaniment in alcohol-related disease even in Third World countries. However, it is probably overlooked as a cause of mental deterioration in many of these patients because of non-specific

symptoms and the difficulty in eliciting neurological signs in the ill patient. A greater clinical awareness is therefore demanded in these patients. Thiamine should form part of the routine management in the alcoholic patient with liver disease, pancreatitis or cardiac failure, even in the absence of neurological deficit.

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